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Original Article

The Effect of Inhaled Milrinone Versus Inhaled Levosimendan in Pulmonary Hypertension Patients Undergoing Mitral Valve Surgery — A Pilot Randomized Double-Blind Study

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Objective: To compare the effects of inhaled milrinone and levosimendan on pulmonary and systemic hemodynamics in patients with pulmonary hypertension.
Design: Prospective, double-blind, randomized controlled study.
Setting: Tertiary care cardiac institute with 650 beds.
Participants: The study comprised 150 adult patients with pulmonary hypertension undergoing mitral valve surgery.
Interventions: Patients were assigned randomly into 1 of the following 3 groups: milrinone (M), levosimendan (L), or control (C); n = 50 per group. In group M, inhaled milrinone (50 μg/kg); in group L, inhaled levosimendan (24 μg/kg); and in group C, normal saline was administered when the patient arrived in the recovery room. Pre-inhalation and post-inhalation hemodynamics (mean arterial pressure [MAP], pulse rate, and systemic vascular resistance [SVR]) were noted until 24 hours of inhalation of the drug. The change in pulmonary artery pressures (pulmonary artery systolic pressure [PASP] and mean pulmonary artery pressure [MPAP]) and the duration for which they remained decreased compared with the control group, were noted.
Measurements and Main Results: MAP, pulse rate, and SVR were comparable in the 3 groups at various time intervals. PASP and MPAP decreased comparably after inhalation of levosimendan and milrinone. However, they reached levels near the control group values after 2.5 to 3 hours in group L and after 0.5 hours in group M.
Conclusions: Because inhaled levosimendan causes a decrease in PASP and MPAP without causing a decrease in SVR and MAP, the authors conclude that inhaled levosimendan is a selective pulmonary vasodilator. It is as effective as milrinone in reducing pulmonary artery pressures. In addition, it has advantage over inhaled milrinone because it is has a longer duration of action.
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Key Words: inhalation; milrinone; levosimendan; pulmonary hypertension; pulmonary artery pressure; systemic vascular resistance

PULMONARY HYPERTENSION (PH) is an important cause of morbidity and mortality in patients with cardiac diseases. PH increases right ventricular (RV) work, which can lead to RV dysfunction after cardiopulmonary bypass.[1–3]

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The presence of RV failure carries a poor prognosis, with a high risk of perioperative mortality ranging from 37% to 90%.[4–6]

For successful management of these patients, factors that can precipitate pulmonary hypertensive crisis should be avoided and drugs to lower pulmonary vascular resistance should be used. Prostacyclin and phosphodiesterase inhibitors, such as milrinone, have been used successfully for that purpose. However, intravenous administration is limited by systemic hypotension because of nonselective vasodilation and by hypoxemia through worsening of intrapulmonary shunt caused by inhibition of hypoxic pulmonary vasoconstriction.[7,8]

These side effects warrant the use of selective pulmonary vasodilators, without systemic effects, in patients with PH. Nitric oxide has been used widely via the inhalational route to selectively dilate the pulmonary vasculature. However, this is expensive, requires specialized equipment, and there is concern regarding its toxicity.[9,10] Physicians who treat PH in the perioperative setting should be aware of the caveats of inhaled nitric oxide (iNO) and iNO alternatives, which include nitric oxide donors, adenylate cyclase stimulators, and phosphodiesterase inhibitors, each of which has its own limitations.

Levosimendan is a pyridazinone dinitrile derivative with positive inotropic and vasodilatory effects and has beneficial effects on myocardial performance. The drug is a calcium-channel sensitizer. In case reports and a few studies, intravenous levosimendan has shown a clear benefit during cardiac surgery in patients with severe PH by reducing pulmonary artery pressure (PAP) and protecting RV contractility.[11–15] Currently, the data for inhaled levosimendan are very limited.[16]

In this prospective, randomized, double-blind study, the acute effects of inhaled milrinone and inhaled levosimendan on pulmonary and systemic hemodynamics were compared in adult patients with PH undergoing mitral valve surgery. The authors hypothesized that the systemic side effects of inhaled levosimendan would be comparable with those of inhaled milrinone and because inhaled levosimendan is long-acting, it could be an additional therapy for the prevention and treatment of pulmonary hypertensive crisis.

The aim of this study was to compare the effect of inhaled milrinone and inhaled levosimendan with placebo in patients with PH undergoing mitral valve surgeries.

Methodology

After receiving Institutional Ethical Committee approval, 150 consecutive adult patients with mitral valve disease and PH undergoing mitral valve surgery were enrolled into this prospective, double-blind, randomized controlled study. Written, informed consent was obtained from all patients.

Inclusion Criteria

The study comprised patients with mitral valve disease and PH undergoing mitral valve surgery. Patients were considered to have PH if their resting pulmonary artery systolic pressure (PASP) was greater than 35 mmHg on their preoperative transthoracic echocardiography.

Exclusion Criteria

- Pediatric patients (age < 18 y)
- Patients unwilling to be part of the study
- Any contraindication for insertion of a pulmonary artery catheter

Sample Size Calculation

Because no study on the use of inhaled levosimendan in PH was available, the authors decided to calculate the sample size from a previous study[15] on the use of intravenous levosimendan in PH. Considering type I error at 5% (2-sided) and power at 80% and using Power and Precision software, version 2 (trial),[17] by taking systolic pulmonary artery pressures (PASP) in 2 groups as 55 mmHg and 48 mmHg with an assumed standard deviation of 12, the sample size obtained was 48 per group. Similarly, taking mean pulmonary artery pressures (MPAP) in 2 groups as 36 mmHg and 33 mmHg with an assumed standard deviation of 5, the sample size obtained was 45 per group. Considering the calculations, a sample size of 50 per group was used.

Patients were assigned randomly into 1 of 3 groups ($n = 50$ in each group) on the basis of a computer-generated randomization table. The randomization scheme was generated by using the Randomization.com website (http://www.randomization.com). The computer-generated group numbers (M, L, or C) were put in serially numbered closed opaque envelopes. A person not related to the study (anesthesia technician) was asked to open the closed envelope containing the computer-generated group number and prepare the drug accordingly. The groups were as follows:

- Group M: Inhaled milrinone (50 μg/kg) was administered when the patient arrived in the postoperative recovery room.
- Group L: Inhaled levosimendan (24 μg/kg) was given when the patient arrived in the postoperative recovery room.
- Group C: Inhaled 0.9% normal saline was administered when the patient arrived in the postoperative recovery room.

The dosage of these drugs was based on their loading dose and what has been used in previous studies. All drugs were administered through a compressor nebulizer (Innovative Medical Devices, New Delhi, India) attached to the inspiratory limb of the ventilator near the endotracheal tube. The nebulizer was filled with the drug by the anesthesia technician, and the nebulizer was covered by dark paper so that the administering anesthesiologist would not know which drug was being administered.

A FloTrac monitor (Edwards Lifesciences, Irvine, CA) was used to monitor the systemic vascular resistance (SVR). Baseline hemodynamic profile (blood pressure, pulse rate,

Table 1
Patient Characteristics

	Group M	Group L	Group C	p Value
Age	40.8 ± 8.17	40.9 ± 7.07	38.7 ± 9.42	0.33
Sex (M:F)	31:19	32:18	30:20	0.92
Ejection fraction	52.6 ± 6.79	54.7 ± 7.33	52.4 ± 6.04	0.18
Mitral valve pathology (MS: MR)	33:17	36:14	32:18	0.67

Abbreviations: C, control; L, levosimendan; M, milrinone; MR, Mitral Regurgitation; MS, Mitral Stenosis.

PAP, and SVR) was obtained immediately after insertion of a pulmonary artery catheter after anesthesia induction. Another reading of the hemodynamic profile was performed after the patient was weaned off cardiopulmonary bypass.

Inotrope use in all patients was guided by hemodynamic data such as mean arterial pressure (MAP), central venous pressure, and intraoperative transesophageal echocardiography to maintain a MAP of around 70 mmHg.

After surgery, the patients were transferred to the postoperative recovery room. At this time the inhaled drug was administered. Pre-inhalation and post-inhalation hemodynamic status were noted. These variables were recorded every half-hour for 8 hours and then hour until 24 hours of drug/saline administration. The decrease in the PASP & MPAP levels and the duration for which they remained decreased from the postoperative values were noted.

Statistical Analysis

One-way analysis of variance was used to test the difference between groups. Univariate analysis of the dichotomous variables encoded was performed using the chi square test with Yates correction if required. Statistical analysis was performed using Statistical Package for Social Science-SPSS for windows ver 10.5 (SPSS Inc. Chicago IL, USA). A p value < 0.05 was considered to be statistically significant.

Results

Patient characteristics were comparable in the 3 groups (Table 1). The hemodynamics (MAP and pulse rate) were comparable in the 3 groups at various time intervals (Figs 1 and 2). The SVR was comparable in the 3 groups at all time intervals (Fig 3).

PASP and MPAP decreased after inhalation of levosimendan and milrinone. However, in group L, they reached levels near the control group values after 3 hours, whereas in group M they returned near the control values after 0.5 hours. (Figs 4 and 5).

Discussion

The authors report the first human experience on the use of inhaled levosimendan. Boost et al[16] conducted an animal study in rats in which they found that prophylactic inhalation of levosimendan improved survival and reduced the release of

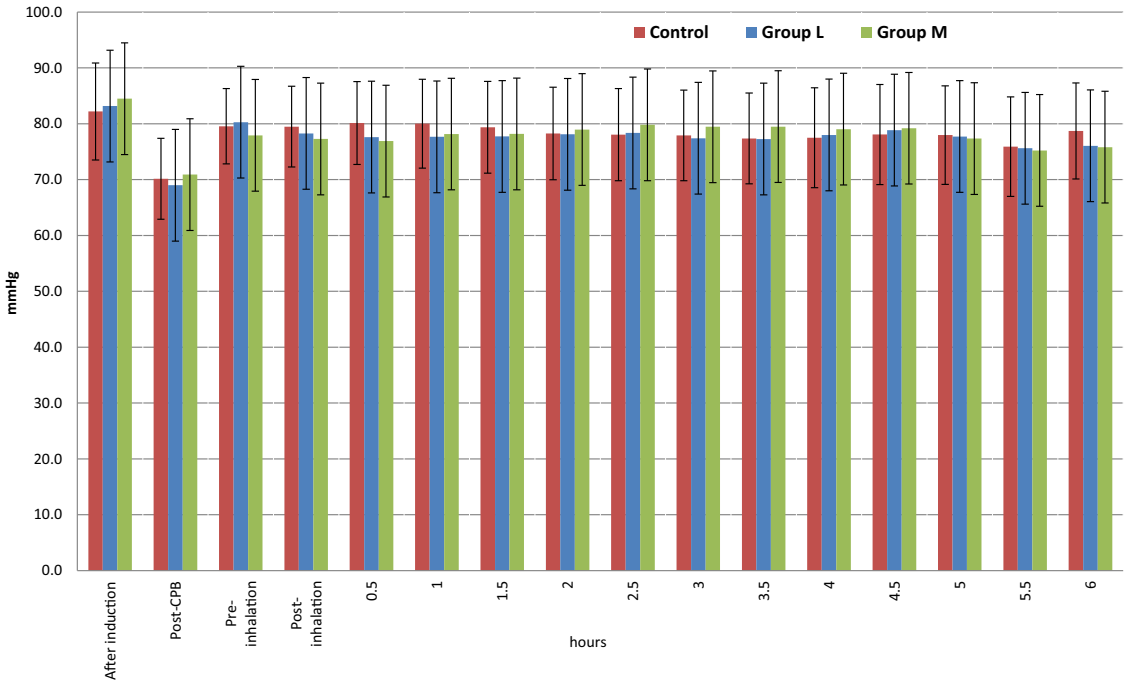

Fig 1. Comparison of mean arterial pressure between the 3 groups at different time intervals. CPB, cardiopulmonary bypass.

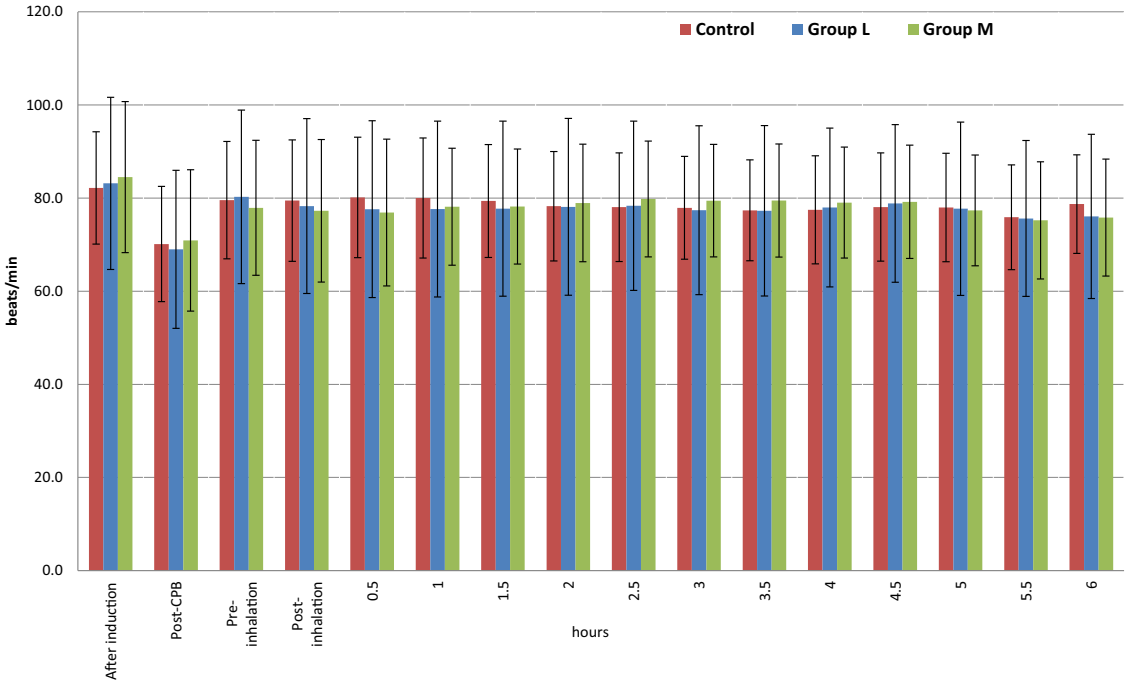

Fig 2. Comparison of pulse rate between the 3 groups at different time intervals. CPB, cardiopulmonary bypass.

inflammatory mediators in an experimental model of ventilator-induced lung injury.

In the present study, the investigators wanted to explore whether inhaled levosimendan decreases PAP, and if it does, to compare the duration of action of this drug with inhaled milrinone. In addition, the investigators wanted to examine the effect of inhaled levosimendan on SVR.

The major findings of the present study were that inhaled levosimendan causes a decrease in PAP in the same way as milrinone does compared with placebo (see Figs 4 and 5). However, although PAP in the milrinone group became comparable with that in the placebo group at 0.5 hour, PAP in the levosimendan group became comparable with that of placebo at the end of 3 hours. This points toward the longer duration of action of inhaled levosimendan compared with inhaled milrinone, which can be viewed as an advantage of inhaled levosimendan over inhaled milrinone. Neither drug had a significant effect on SVR, which points toward the

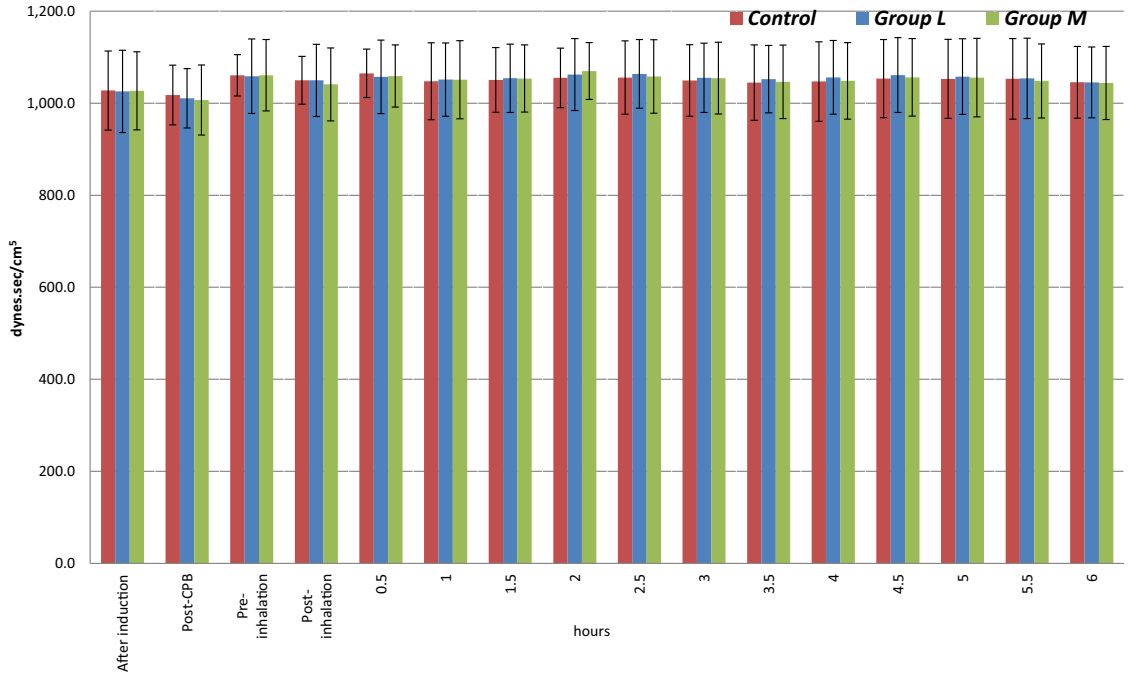

Fig 3. Comparison of systemic vascular resistance between the 3 groups at different time intervals. CPB, cardiopulmonary bypass.

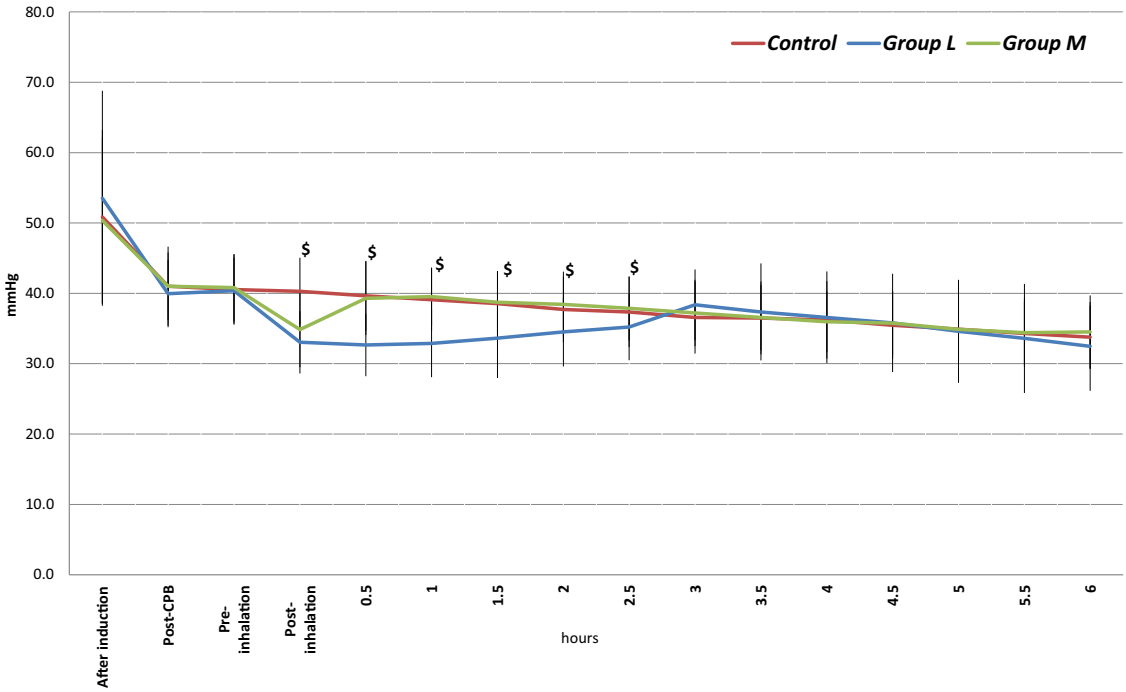

Fig 4. Comparison of systolic pulmonary artery systolic pressure (PASP) between the 3 groups at different time intervals. $, statistically significant difference; CPB, cardiopulmonary bypass.

drugs' selective pulmonary vasodilatory action. The effects of both drugs were not associated with systemic hypotension (see Fig 1).

The dose of inhaled milrinone and inhaled levosimendan was based on each drug's loading dose. In one of the early trials on inhaled milrinone, Haraldsson et al[18] used stepwise increasing concentrations of milrinone (0.25, 0.5, and 1 mg/mL) administered by inhalation for 3 subsequent 10-minute periods (0.25-0.3 mL/min) and found that the maximal effect was with the largest concentration. Sablotzki et al[19] used a dose of inhaled milrinone of 2 mg in heart transplantation patients based on the recommendations for the loading dose of milrinone in patients with severe heart failure (25-50 μg/kg) and the study by Haraldsson et al[18] Similarly,

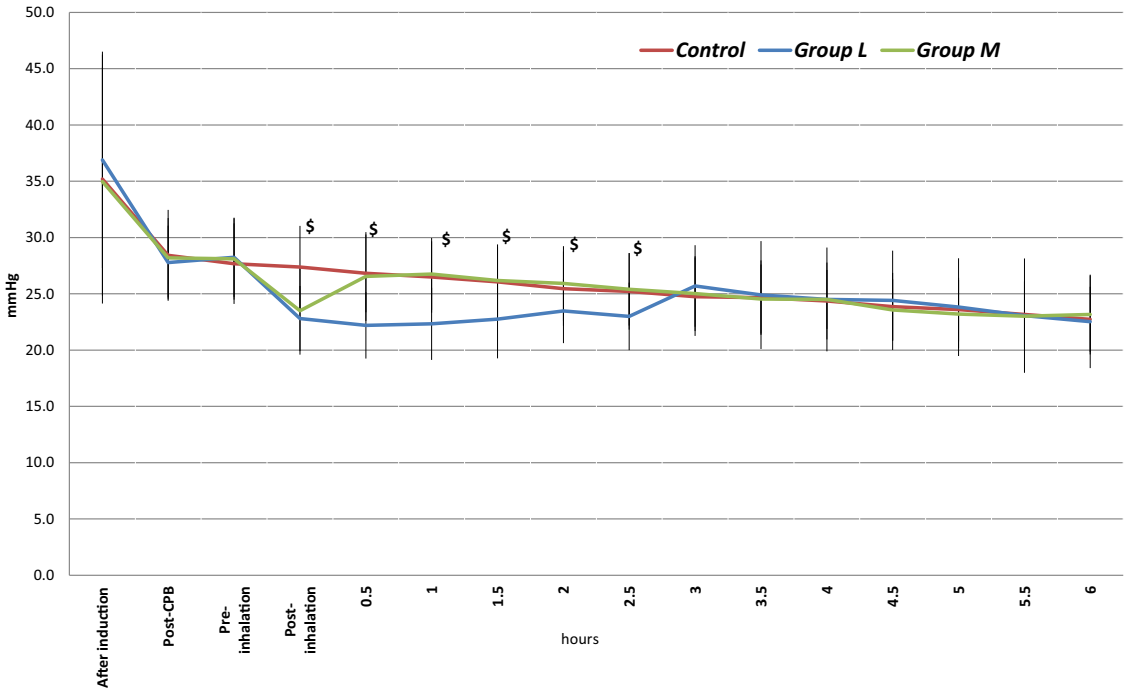

Fig 5. Comparison of Mean Pulmonary Artery Pressure (MPAP) between the 3 groups at different time intervals. $, statistically significant difference; CPB, cardiopulmonary bypass.

Singh et al[20] used a dose of 50 μg/kg of inhaled milrinone in children with congenital heart disease and PH. Because there is no literature available for the use of inhaled levosimendan in humans, the investigators decided to use the loading dose of levosimendan (ie, 24 μg/kg).

In a recent study, Mishra et al[15] compared the effects of intravenous levosimendan and intravenous milrinone in cardiac surgery patients with PH and left ventricular dysfunction. The major side effect of using intravenous levosimendan was a decrease in SVR leading to systemic hypotension. The present study investigators hypothesized that inhaled levosimendan may have a selective pulmonary vasodilatory effect.

As such, the investigators could not find any literature in which inhaled levosimendan had been used to decrease PAP levels in patients with PH. Hence, the investigators decided to conduct the present study to explore the selective pulmonary vasodilatory effect of inhaled levosimendan.

In the present study, inhaled levosimendan caused a 21% decrease in MPAP. In a study by Amor et al,[14] intravenous levosimendan decreased MPAP by 15%. In another study, Mishra et al[15] showed a 25% decrease in MPAP caused by intravenous levosimendan. This suggests that inhaled levosimendan is as effective as intravenous levosimendan in reducing MPAP.

The PASP and MPAP were lower for a duration of 3 hours in the levosimendan group as opposed to 0.5 hour in the milrinone group after inhalation of the respective drug, when both were compared with the control group. This suggests a longer duration of action of inhaled levosimendan.

The investigators could not find any literature about the duration of action of inhaled levosimendan, although intravenous levosimendan has been proven to be quite long-acting. Martyniuk et al[11] found that at 24 hours after initiation of levosimendan infusion, there was a substantial decrease in PASP, MPAP, mean right atrial pressure, and pulmonary vascular resistance (PVR). Even at 12 weeks after termination of levosimendan infusion, the improved functional status was preserved in patients with idiopathic PH. The effects are long-lasting due to the active metabolite OR-1896, which has an elimination half-life of 70 to 80 hours in patients with heart failure (New York Heart Association functional class III-IV).[21]

In the present study, milrinone decreased MPAP by 16%. In an earlier study by Haraldsson et al,[18] the decrease in MPAP by inhaled milrinone (1 mg/mL at 0.25-0.3 mL/min over 10 min) was only 6%. However, the sample size in that study was too small (n = 9). Results similar to those of the present study were found by Sablotzki et al,[19] who demonstrated a 13% decrease in MPAP in patients with PH who received inhaled milrinone and underwent heart transplantation with the same number of patients in the study by Haraldsson et al (n = 9). Similar results also were found in a study by Singh et al,[20] in which inhaled milrinone decreased MPAP by 14.9% in children with congenital heart disease who experienced PH (n = 18).

Haraldsson et al[18] found that PAP returned to baseline within 20 minutes after termination of milrinone inhalation. Similarly, Sablotzki et al[19] found that PAP returned to baseline values after 30 minutes. The results match those of the present study in which the PAP returned to the baseline in 0.5 hour.

Amor et al[14] found that the use of intravenous levosimendan was associated with a significant decrease in SVR. In another study, Mishra et al[15] compared the effect of intravenous levosimendan with intravenous milrinone in patients with PH and left ventricular dysfunction undergoing cardiac surgery. The authors observed a significant decrease in SVR with the use of levosimendan and milrinone, which was a major side effect. Similarly, in another study conducted by Wang et al,[22] the authors found SVR to be significantly higher in the inhaled milrinone group when they compared inhaled milrinone with intravenous milrinone.

In the present study, there was no significant decrease in SVR with the use of inhaled levosimendan and inhaled milrinone. Although there is no literature available for the effect of inhaled levosimendan on SVR, the effect of inhaled milrinone on SVR has been studied. Haraldsson et al[18] found that inhaled milrinone does not have an effect on SVR, although it decreases the PVR, suggesting its selective pulmonary vasodilation. Similarly, Sablotzki et al[19] found that inhaled milrinone did not have a significant effect on the SVR index. However, in the study by Singh et al,[20] there was a significant decrease in the SVR index. Inhaled milrinone caused a decrease in both the PVR index and SVR index, but the effect on the SVR index (−18%) was small compared with the effect on the PVR index (−68%), highlighting a more selective effect on pulmonary vasculature when given through the inhaled route. Their study was performed on children with acyanotic congenital heart disease experiencing pulmonary artery hypertension in the catheterization laboratory. The patient population in the present study is much different from their cardiac catheterization laboratory pediatric population. The more dynamic nature of PVR and SVR in their patient population, with a different pathophysiology contributing to PH, could be the possible reason for this result.

MAP was comparable in the 3 groups and there was no hypotension in any group after inhalation of the drug. Amor et al[14] found a significant decrease in MAP with the use of intravenous levosimendan. Similarly, Mishra et al[15] found a decrease in MAP with both intravenous levosimendan and intravenous milrinone. Even though there is no available literature for inhaled levosimendan, studies on inhaled milrinone show a result similar to the present study. Haraldsson et al[18] did not find a significant decrease in MAP with the use of inhaled milrinone. Similarly, Sablotzki et al[19] did not find a significant decrease in MAP in their study. Similar results were seen in the study conducted by Singh et al.[20]

One of the limitations of the present study was that the authors did not know the comparable doses of inhalational milrinone and levosimendan due to scarcity of literature. Ideally, a dose-finding study should have been performed first. The investigators decided to use the loading doses of milrinone and levosimendan as has been done in previous studies on inhalational pulmonary vasodilators.

A word of caution must be noted on the potential for acute pulmonary toxicity if levosimendan is administered over a

prolonged duration.[23] Acute toxicity is defined as inhalation for at least 4 hours[24] and occurs if a large concentration of drug is inhaled for a long period without monitoring. The same holds true for iNO, sodium nitroprusside, nitroglycerin, and milrinone, which have been described to have a similar or even greater potential for acute pulmonary toxicity.[23] Direct pulmonary toxicity with levosimendan has not been reported in the literature. Simply put, being toxic "to the lungs" is different from being toxic "through the lungs." Levosimendan may be acutely toxic "through the lungs," which means it may cause a lot of pulmonary vasodilation and hemodynamic collapse if a large unregulated amount of levosimendan is inhaled, just like with the other pulmonary vasodilators.

Conclusion

From the present study, the investigators conclude that inhaled levosimendan is a selective pulmonary vasodilator. It provides a superior choice over the nonselective intravenous vasodilators because of its minimal effects on SVR and MAP. It is as effective as milrinone in reducing the PAP levels compared with placebo. In addition, it has an advantage over inhaled milrinone because it is has a longer duration of action.

Based on the aforementioned results, the investigators suggest administering levosimendan nebulization postoperatively after every 2.5 to 3 hours in patients with PH undergoing mitral valve surgery for better management of PH.

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